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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,047	MEARES ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,8,10-24,26,27,30 and 33-43* is/are pending in the application.

4a) Of the above claim(s) *16-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,8,10-15,24,26,27,30 and 33-42* is/are rejected.

7)☒ Claim(s) *43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 4/15/2009 in response to the previous Non-Final Office Action (10/16/2008) is acknowledged and has been entered.

Claims 1, 6, 8, 10-24, 26-27, 30 and 33-43 are pending.

Claims 16-23 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1, 6, 8, 10-15, 24, 26-27, 30 and 33-43 are currently under consideration.

Rejections/Objections Withdrawn:

The objection of Claims 6, 8 and 40-42 under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of Applicants amendments.

Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, the Examiner acknowledges Applicants amendment to claim 37. However, similar to the previous rejection, it is unclear whether the antigen recognition domain of said antibody has a second sequence. In the same way, it is unclear what the 1st sequence of said antibody is since the second sequence has been defined by the claims.

(Note: In order to expedite prosecution, it appears to the Examiner that Applicants may be attempting to define the light chain variable region, e.g., SEQ ID NO: 1, and heavy chain variable

region of the antibody, e.g., SEQ ID NO: 5, in a round about way. It this is true, it is suggested that Applicants amend the claim to recite, wherein said antibody has a light chain variable region having at least 95%... and a heavy chain variable region having at least 95%....)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 8, 10-15, 24, 26-27, 30 and 33-42 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

In the instant case, the claim 1 is inclusive of a genus of bispecific antibodies comprising an antigen recognition domain that recognizes a macrocyclic chelate and a targeting moiety that specifically binds to a cell surface receptor or cell surface antigen on a cancer cell. Claim 37 further limits the antibody to having a first sequence having at least 95 % sequence identity to SEQ ID NO: 1 and a second sequence having at least 95% sequence identity to SEQ IDNO: 5. Thus, claim 1 and 37 broadly encompasses antibodies having variations within the 6 CDR regions, but are still capable of binding to a macrocyclic metal chelate and a tumor associated antigen. However, the written description in this case only sets forth an isolated antibody or fragment thereof, comprising a first amino acid sequence that is 100% identical to SEQ ID NO: 1, and a second amino acid sequence

that is 100% identical to SEQ ID NO: 5, wherein one arm of the antibody binds to a tumor antigen and a second arm binds to a tumor associated antigen or a macrocyclic metal chelate.

For example, the specification teaches that after inspection of the crystal structure of the 2D12.5, e.g., light chain of SEQ ID NO: 1 and heavy chain of SEQ ID NO: 5, bound to its hapten DOTA, a number of cysteine residues were introduced at positions 53, 54 and 55 of the heavy chain and position 53 of the light chain. The further teaches determining the scope of the monoclonal antibody, 2D12.5, e.g., light chain of SEQ ID NO: 1 and heavy chain of SEQ ID No: 5. In particular, the specification teaches that the monoclonal antibody 2D12.5 binds not only to Y-DOTA but also DOTA complexes of all the lanthanides. Thus while the specification teaches an isolated antibody or fragment thereof, comprising a first amino acid sequence that is 100% identical to SEQ ID NO: 1, and a second amino acid sequence that is 100% identical to SEQ ID NO: 5 and binds to Y-DOTA or all DOTA complexes with all of the lanthonides, the specification appears to be silent on the binding affinities to DOTA of other antibodies comprising a first amino acid sequence that is at least 95% identical to SEQ ID NO: 1 and a second amino acid sequence that is at least 95% identical to SEQ ID NO: 12, or alternatively, the binding affinities to DOTA of other antibodies comprising a heavy chain variable region comprising a single amino acid substitution in any one of CDR1, CDR2, and CDR3 of SEQ ID NO: 5, and a light chain variable region comprising a single amino acid substitution in any one of CDR1, CDR2 and CDR3 of SEQ ID NO: 1.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently

detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of antibodies that encompass the genus that bind DOTA nor does it provide a description of structural features that are common to the antibodies. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of one species of antibody is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of antibodies, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species). Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is

required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Therefore, only an isolated antibody comprising a first sequence that is 100% identical to SEQ ID NO: 1 and a second sequence that is 100% identical to SEQ ID NO: 5, wherein the antibody binds to DOTA , but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In response to this rejection, Applicants assert that the antigen recognition domain, as claimed, is defined functionally and requires more than simply binding to a macrocyclic metal chelate. For example, Applicants contend that the antigen recognition domain recognizes a macrocyclic metal chelate and further, comprise a reactive site within the structure of the antibody that is not present in the wildtype of the antibody, wherein the active site is in a position within the antigen recognition domain. With regards to the macrocyclic metal chelate, Applicants contend that the macrocyclic metal chelate, Applicants assert that the macrocyclic metal chelate comprises substituted or unsubstituted 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), and comprises a reactive functional group with a reactivity complementary to said antibody reactive site. Looking to the specification, Applicants assert that the specification provides the sequences of multiple heavy chains and light chains that bind DOTA. Specifically, Applicants assert that Figure 2 and 4 provide the sequences of the variant heavy and light chain polypeptides, respectively. As such, Applicants submit that the specification provides antibody heavy and light chains with different sequences.

These arguments have been carefully considered, but are not found persuasive.

In the instant case, the Examiner acknowledges and does not dispute Applicants assertions that the antigen recognition domain of the claimed antibody is defined functionally and requires more than simply binding to a macrocyclic chelate. Moreover, the Examiner acknowledges and does not dispute Applicants assertions that the Figures 2 and 4 set forth the amino acid sequence of the light and heavy chain of six different antibody constructs. However, the Examiner recognizes that

claim 1 and 37 broadly encompasses antibodies having variations within the 6 CDR regions, but are still capable of binding to a macrocyclic metal chelate and a tumor associated antigen. For example, Claim 37 recites that the said antigen recognition domain of said antibody has a first sequence having at least 95% sequence identity with SEQ IDNO: 1, and comprises CDR1 having the amino acid sequence of SEQ IDNO: 2 and CDR3 having the sequence of SEQ ID NO: 4, and wherein said antibody has a second sequence having at least 95% sequence identity with SEQ ID NO: 5, and comprises CDR1 having the amino acid sequence of SEQ ID NO: 6 and CDR3 having the sequence of SEQ ID NO: 8. Thus, claim 1 and 37 broadly encompasses antibodies having variations within the two CDR2's, but are still capable of binding to a macrocyclic metal chelate and a tumor associated antigen. Thus, while the antigen recognition domain of the antibody is claimed by function, as in claim 1, and further, by amino acid sequence which encompass variations within the two CDR regions of the light and heavy chain, it is well established in the art that the formation of an intact antigen-binding site of all antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, Fundamental Immunology, (textbook), 1993, pp. 292-295), under the heading "Fv Structure and Diversity in Three Dimensions", of record). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequence of the heavy and light chain variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Proc. Natl Acad. Sci. USA 1982; 79: 1979, of record). Rudikoff et al. teach that an alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Accordingly, one of skill in the art would not accept the disclosure as representative of possession of the claimed genus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6, 8, 10-15, 24, 26-27, 30, 33-36 and 38-39 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (WO 99/66951, of record) in view of Chmura et al. (PNAS 2001; 98: 8480-8484, of record).

Hansen et al. teach a method of treating diseased tissues in a patient, comprising: (a) administering to a patient a bi-specific antibody or antibody fragment having at least one arm that specifically binds to a targeted tissue and at least one arm that specifically binds a targetable conjugate; (b) optionally, administering to said patient a clearing composition, and allowing said composition to clear non-localized antibodies or antibody fragments from circulation; and (c) administering to said patient a first targetable conjugate which comprises a carrier portion which comprises or bears at least one epitope recognizable by said at least one other arm of said bi-specific antibody or antibody fragment, and one or more therapeutic agents (page 58, claim 1 of WO document). With regards to the targetable conjugate's epitope, the WO document teaches (page 9, lines 30-33) that the epitope includes, but is not limited to, a hapten. With regards to the hapten, Hansen et al. teach (page 10, line 2 and page 34, lines 27-28) that haptens include, but are not limited to, chelators such as DPTA and DOTA. For example, the WO document teaches (page 35, lines 7-11) a method of treating CEA-expresing tumors, wherein a bi-specific antibody with at least one arm, which specifically binds to CEA, and at least one arm, which specifically binds the targetable conjugate whose hapten is a conjugate of yittruim-DOTA is administered to a patient. With regards to the bi-specific antibody which recognizes CEA and a metal chelate such as DOTA, the WO document teaches (page 10, lines 26-33) that the bi-specific antibody is generated by derivatizing an anti-CEA $F(ab')_2$ mAB with a hydrazide-maleimide cross-linker and coupling said derivatized anti-CEA $F(ab')_2$ to an anti-chelate Fab'-SH. Moreover, Hansen et al. teach (page 24, lines 24-33) that

chelators, such as DOTA, may be conjugated to the carrier portion of a targetable conjugate by generating a reactive functional group such as carbodiimide and coupling the carbodiimide to the peptides free amines. Thus, while Hansen et al. does not teach a macrocyclic metal chelate comprising four nitrogen atoms as shown in the formula of claim 6 or an S configuration DOTA, the referenced limitations are an inherent structural feature of DOTA as evidenced by Sigma-Aldrich (see attached document of record). Thus, the claimed antibody appears to recognize the same macrocyclic metal chelate as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that a product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Hansen et al. does not explicitly teach that that the antibody comprises a reactive site within the structure of the antibody that is not present in the wildtype of said antibody, wherein said reactive site is in a position within said antigen recognition domain. Nor does Hansen et al. teach that the macrocyclic DOTA contain a functional group which is reactive with the reactive site of the antibody.

Chmura et al. teach a method of producing antibodies having infinite affinity with a ligand, wherein the antibodies comprise a chemically reactive site such as a cysteine near the ligand-binding site of the antibody; and the ligand comprises an electrophilic substituent designed to form a stable thioether bond on reaction with the cysteine side chain of the antibody (Title and page 8480, 2nd column, 3rd full paragraph and 4th full paragraph). While the reference teaches that the chemical manipulation of affinity is applicable to other biological binding pairs, the antibody used was the anti-chelate antibody CHA255 and the ligand used was (S)-benzyl-EDTA-indium chelates since the anti-chelate antibody possess high affinity for (S)-benzyl-EDTA-indium chelates and exquisite specificity for these small molecules (page 8480, 2nd column, 3rd full paragraph and 4th full paragraph). In particular, the reference teaches that a slow rate of dissociation is particularly important for in vivo targeting application, where a targeted therapeutic drug requires a long period on the target to be effective (page 8480, 2nd column, 1st full paragraph). However, the reference

teaches that most natural antibodies, as well as engineered fragments, against small molecule possess only a single ligand binding site; and therefore, only remain bound to its ligand for an average period of a few minutes to a few hours (page 8480, 2nd column, 1st full paragraph). As such, the reference teaches that the surest way to prolong the lifetime of a complex is to make a covalent bond between its components (page 8480, 2nd column, 2nd full paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to modify the anti-chelate antibody and chelate, e.g., DOTA, used in the method taught by Hansen et al. in view of the teachings of Chmura et al.. One would have been motivated to do so because Chmura et al. teach a method of generating an antibody having infinite affinity for a ligand which is applicable for to other ligand binding pairs, wherein the antibody forms a covalent bond with the ligand which prolongs the lifetime of the complex. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the anti-chelate antibody and chelate, e.g., DOTA, used in the method taught by Hansen et al. in view of the teachings of Chmura et al., one would achieve a method of prolonging the lifetime of the complex at the target site in vivo.

In response to this rejection, Applicants assert that Hansen teaches bi-specific antibody conjugates, wherein in some embodiments, indicates that one arm of the bi-specific antibody binds a hapten, which can include chelators. However, Applicants maintain that while Hansen mentions that DOTA may be useful in a list of potentially useful chelators, there is no specific teaching that DOTA could be a direct target of an antibody in a bifunctional antibody conjugate. Additionally, Applicants assert that Hansen notes that the "arm of the bsAb that binds to the low MW hapten must bind with high affinity (see p. 2 of Hansen). However, Applicants assert that Hansen also notes the problems associated with this high affinity, namely that "[b]ecause the Abs were raised against the chelators and metal chelate complexes, they have remarkable specificity for the complex against which they were originally raised... This great specificity has proven to be a disadvantage in one respect, in that other nucides... can not be readily substituted into available regents for alternative uses." In contrast, Applicants contend that the present claims are directed to methods that result in a marked increased affinity, e.g., a covalent attachment, between the bi-functional antibody and the macrocyclic metal chelate. Thus, Applicants remind the Examiner that "It is improper to combine references were the references teach away from the combination; and further

submit that because Hansen cautions against antibodies that are too specific one of skill in teh art would not have been motivated to produce an antibody for use in the method of Hansen wherein the antibody had a marked increased affinity, e.g., covalent attachment, between the antibody and the hapten. Moreover, Applicants assert that while the Examiner has relied on Chimura to provide motivation to combine Hansen and Chmura, Applicants respectfully submit that this is in appropriate in view of the above arguments.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertions pertaining to the teachings of Hansen et al., the Examiner acknowledges and does not dispute Applicants contention that Hansen et al. teach a bi-specific antibody, with one arm binding to a peptide carrier attached to a metal chelate or chelating agent, wherein the carrier peptide is the hapten, e.g., the antibody is actually raised against, and recognizes, the peptide carrier portion of the targetable conjugate (in several examples the peptide), not the chelate (see for example, page 12, lines 3-6 and page 23, lines 4-8). However, the Examiner recognizes that this is only one embodiment taught by Hansen and the antibody does not appear to be limited to just recognizing the carrier peptide. For example, Hansen et al. teach the following:

> The present invention provides a bi-specific antibody or antibody fragment having at least one arm that specifically binds a targeted tissue and at least one other arm that specifically binds a targetable conjugate. The targetable conjugate comprises a carrier portion which comprises or bears at least one epitope recognized by at least one arm of the bi-specific antibody or antibody fragment. In a preferred embodiment, the epitope is a hapten. In an alternative embodiment, the epitope is a part of the carrier. (page 9, last paragraph bridging page 10)

In view of this, it is clear that Hansen et al. is not limited to a bispecific antibody, with one arm binding to a peptide carrier attached to a metal chelate as asserted by Applicants, but encompass's bispecific antibodies with one arm which recognizes the hapten itself. Moreover, Hansen et al. teaches that examples of recognizable haptens include, but are not limited to, chelators, such as DTPA, fluorescein isothiocyanate, vitamin B-12 and other moieties **to which specific antibodies can be raised** (emphasis added) (page 10, lines 1-4). Additionally, Hansen et al. teaches antibodies which recognize a metal-DOTA complex. For example, Hansen et al. teach the following:

> In still other embodiments, the bi-specific antibody-directed delivery of therapeutics or prodrug polymers to *in vivo* targets can be combined with bi- specific antibody delivery of radionuclides, such that combination chemotherapy and radioimmunotherapy is achieved. Each

> therapy can be conjugated to the targetable conjugate and administered simultaneously, or the nuclide can be given as part of a first targetable conjugate and the drug given in a later step as part of a second targetable conjugate. In one simple embodiment, a peptide containing a single prodrug and a single nuclide is constructed. For example, the tripeptide Ac-Glu-GIy-Lys-NH2 can be used as a carrier portion of a targetable conjugate, whereby SN-38 is attached to the gamma glutamyl carboxyl group as an aryl ester, while the chelate DOTA is attached to the epsilon amino group as an amide, to produce the complex Ac-Glu(SN-38)-GIy- Lys(DOTA)-NH2. The DOTA chelate can then be radiolabeled with various metals for imaging and therapy purposes including In-Ill, Y-90, Sm-153, Lu- 177 and Zr-89. **As the metal-DOTA complex may represent the recognizable hapten on the targetable conjugate, the only requirement for the metal used as part of the DOTA complex is that the secondary recognition antibody also used recognizes that particular metal-DOTA complex at a sufficiently high affinity. Generally, this affinity (log K~) is between 6-11** (emphasis added) (page 34, lines 13-31).

Thus, while the Examiner does not dispute Applicants contention that Hansen et al. teaches bispecific antibodies with one arm which binds to an epitope present in a peptide carrier which is conjugated to a metal chelate, the Examiner recognizes that Hansen et al. also teaches bispecific antibodies with one arm which recognize particular metal-chelate complexes such as DOTA with sufficiently high affinity. In response to Applicants assertions of teaching away from the claimed invention, the Examiner acknowledges and does not dispute that Hansen on page 2., 2nd full paragraph of the Related art section, teaches:

> Of interest with this approach are bsAbs that direct chelators and metal chelate complexes to cancers using Abs of appropriate dual specificity. The chelators and metal chelate complexes used are often radioactive, using radionuclides such as cobalt-57 (Goodwin et al., U.S. Pat. No. 4,863,713), indium-111 (Barbet et al., U.S. Pat. No. 5,256,395 and U.S. Pat. No. 5,274,076, Goodwin et al., J. Nucl. Med., 33:1366 1372 (1992), and Kranenborg et al., Cancer Res (suppl.), 55:5864s 5867s (1995) and Cancer (suppl.) 80:2390 2397 (1997)) and gallium-68 (Boden et al., Bioconjugate Chem., 6:373 379, (1995) and Schuhmacher et. al., Cancer Res., 55:115 123 (1995)) for radioimmuno-imaging. Because the Abs were raised against the chelators and metal chelate complexes, they have remarkable specificity for the complex against which they were originally raised. Indeed, the bsAbs of Boden et al. have specificity for single enantiomers of enantiomeric mixtures of chelators and metal-chelate complexes. This great specificity has

> proven to be a disadvantage in one respect, in that other nuclides such as yttrium-90 and bismuth-213 useful for radioimmunotherapy (RAIT), and gadolinium useful for MRI, cannot be readily substituted into available reagents for alternative uses. As a result iodine-131, a non-metal, has been adopted for RAIT purposes by using an I-131-labeled indium-metal-chelate complex in the second targeting step. A second disadvantage to this methodology requires that antibodies be raised against every agent desired for diagnostic or therapeutic use.

However, the Examiner is confused on how this teaching in the Related Art section of Hansen constitutes a teaching away from the claimed invention since it appears from Hansen (page 3, 1st full paragraph) that the immunological reagent, e.g. an antibody, of Hansen is different from the related art. As such, the rejection is maintained.

New Claim 43 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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